not treated with said agent, wherein any differences therebetween are transcripts of genes whose activation is effected by phosphorylation of Smad1 or Smad-5.

REMARKS

The Examiner contends that Applicants have not complied with one or more condition for receiving the benefit of an earlier filing date under 35 U.S.C. § 120. Applicants have amended the application such that the first page of the specification refers to the prior applications, i.e., "This application is a continuation-in-part of application no. 09/039,177 filed March 18,1998 which is a continuation-in-part of application 08/436,265, which is a National Stage of PCT/GB93/02367 filed November 17, 1993." Support for this amendment is found in the Declaration and on the transmittal form filed concurrently with this application.

The Examiner states that the Declaration/Oath is defective because it contains changes that are not initialed or dated. Applicants submit concurrently herewith a replacement Declaration executed by the inventors.

The Examiner requests clarification of the information recited on the filing receipt. The continuing data as claimed by applicants should recite:

This appln is a CIP of 09/039,17 03/13/98

which is a CIP of 08/436,265 10/30/95

The Examiner also contends that the application is not in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. Applicants submit concurrently herewith a paper copy and a C.R.F. of the sequence listing and a statement under 37 C.F.R. § 1.821 (f) and (g).

The Examiner has objected to the labeling of Figure 3. Applicants will provide an amended Figure 3 upon receiving a Notice of Allowance.

Claim 15 stands rejected under 35 U.S.C. § 112, second paragraph for purportedly being indefinite. The Examiner contends it is not clear what is being inhibited and suggests amending claim 15 to recite "binding of TGF-β to ALK-1". Although applicants believe that claim 15 is not unclear and would be readily understood by one of skill in the art, applicants have amended claim 15 as suggested by the Examiner to expedite prosecution. Applicants make this amendment of claim 15 not for reasons of patentability but solely to clarify the language of the claim by adopting the Examiner's suggestion. The amendment does not and is not intended to alter the scope of the claim.

Claim 20 also stands rejected under 35 U.S.C. § 112, second paragraph for purportedly being indefinite. In particular, the Examiner contends that the term "TGF-receptor" does not make clear which receptor is intended. The Examiner suggests amending the claim to recite "TGF-β receptor". Although applicants believe that claim 20, read within the context of the specification is clear and would be readily understood by one of skill in the art, applicants have amended claim 20 to incorporate the Examiner's suggestion. Applicants make this amendment of claim 20 not for reasons of patentability but solely to clarify the language of the claim by adopting the Examiner's suggestion. The amendment does not and is not intended to alter the scope of the claim.

In view of the amendments to claims 15 and 20 applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims.

Claims 14-16, 18, and 20 stand rejected under 35 U.S.C. § 102(b) for purportedly being anticipated by Takahashi et al. In particular, the Examiner contends that the claimed method is inherent in Takahashi et al. because Takahashi et al. use an anti-TGF-β antibody, which the Examiner speculates would interfere with TGF/ALK-1 interaction. The Examiner further speculates that the purported interference would in turn inhibit phosphorylation of the Smads. Applicants disagree.

> Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency.

Continental Can co v. Monsanto 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

The Examiner concludes that the antibody disclosed by Takahashi et al. would inhibit the binding of TGF-β to ALK-1 and would in turn interfere with TGF-β -mediated phosphorylation of Smad-1. However, Takahashi et al. does not disclose the binding characteristics of the antibody. Though Takahashi touts that the antibody as a "TGF-β neutralizing antibody" they do not provide any information on how the "neutralization" was effected. Those of skill in the art appreciate that TGF-β has many functions and there is no information as to which functions of TGF-β were "neutralized." Takahashi et al. does not teach the antibody inhibits the interaction of ALK-1 and TGF-β. It is the Examiner who concludes without providing any objective evidence that the antibody used by Takahashi et al. prevents the binding of ALK-1 and TGF-β and the subsequent phosphorylation of Smad-1 or Smad-5.

Even if arguendo, the Takahashi et al. antibody binds to TGF-β it is only a possibility that this binding may prevent TGF-β from interacting with ALK-1 and is only a possibility that such binding would inhibit phosphorylation of Smad-1. Takahashi et al. does not investigate the effect of their antibody on the interaction of TGF-β and ALK-1 or the effect on the phosphorylation of Smad-1or Smad-5. The Examiner concludes that the Takahashi et al. anti-TGF-β-antibody, which enhances proliferation of HUVEC cells, would also prevent the interaction of TGF-β and ALK-1 and the subsequent phosphorylation of Smad-1 or Smad-5. The mere speculation that a certain thing may result from a given set of

circumstances is not sufficient to establish inherency. Continental Can co v. Monsanto, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

In view of the foregoing remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(b).

Claim 28 stands rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over Hopkins in view of Kokame. In view of the following remarks applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner states "one of ordinary skill in the art would be motivated to combine [Kohame and Hopkins] in order to study the role of TGF-β-induced novel gene transcripts underlying mechanisms of platelet-induced vascular injury or diseases such as thrombosis."(Office Action page 9, lies 14-17). However, the standard for an obviousness rejection is not whether the art could have been modified to suggest applicants' invention, the standard is whether the art itself would have been so modified. This determination cannot be made based on hindsight.

> "There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge can not come from the applicant's invention itself."

In re Oetiker, 24 USPQ2d 1443, 1446 (CAFC, 1992)

> Although couched in terms of combining teachings found in the prior art, the same inquiry must be carried out in the context of a purported obvious "modification" of the prior art. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

In re Fritch 23 USPQ2d 1780(1992)

Nothing in Hopkins or Kohame suggests their combination and neither Hopkins or Kohame, alone or in combination, provide the suggestion or motivation to modify their teachings as suggested by the Examiner.

Applicants invention relates to a method for the identification of genes whose expression is affected by phosphorylation of Smad-1 or Smad-5 by treating a sample of cells, which express ALK-1, with an agent that inhibits or activates ALK-1. Applicants have demonstrated that ALK-1 in response to TGF-β phosphorylates Smad-1 and Smad-5.

In contrast, Hopkins is specifically concerned with the regulation of a single known gene product, PAI-1, in Hep G2 cells and the analysis of platelet lysates to identify mediators of PAI-1 expression within those lysates. Hopkins is not concerned with identifying other genes that are regulated by components of platelet lysates. Hopkins does not disclose whether the Hep G2 cells express ALK-1, Smad-1 or Smad-5, or if PAI-1 is phosphorylated by Smad-1 or 5. Hopkins does not explicitly or implicitly suggest modifying their disclosure to develop a method for identifying genes activated by phosphorylated Smads in ALK-1 containing cells. Thus, there is no motivation in Hopkins to develop a method for identifying genes, in any cell type, whose activation is effected in response to Smad phosphorylation by contacting a cell which expresses ALK-1 with an agent that inhibits or activates ALK-1. Kohame does not compensate for the deficiencies of Hopkins.

Kohame is only interested in the effects of homocysteine on gene expression. There is no suggestion in Kohame to use any other agent; to do so would defeat Kohame's purpose. There is also no suggestion in Kohame that homocysteine would have any effect on ALK-1 or that it is in any way involved with Smad-1 or Smad-5 in regulating gene expression.

Prior to applicants' disclosure there was no evidence that ALK-1 phosphorylated Smad-1 and Smad-5 in response to TGF-β. Without the knowledge that ALK-1 phosphorylates Smad-1 and Smad-5 there is no reasonable expectation that a disruption in

the TGF-β/ALK-1 interaction would affect phosphorylation of Smad-1 or Smad-5. Thus, there is no motivation in Kohame or Hopkins, alone or in combination, to use any agent, e.g., TGF-β, to inhibit or activate ALK-1 in a method to identify genes whose activation is effected by phosphorylated Smad-1 or Smad-5.

The Examiner contends that Kohame teaches differential display to study the mechanisms by which homocysteine may promote vascular diseases. The Examiner then makes two modifications to Kohame: (1) rather than using homocysteine, the focal point of Kohame's experiments, the Examiner suggests using platelet lysates and (2) rather than assaying the expression of PAI, the focal point of Hopkins experiments, the Examiner suggests assaying gene expression in general. The Examiner contends that the motivation for these modifications would be to study the role of TGF-β-induced novel gene transcripts underlying the mechanisms of platelet-induced vascular injury or diseases such as thrombosis. However, these modifications are suggested by the Examiner and not suggested by the cited art. Kohame is interested only in the effects of homocysteine on HUVECs, there is no motivation to use another agent, and Hopkins is only interested in the expression of PAI, there is no motivation to analyze other genes. As such, their combination does not suggest the method as claimed, i.e., a method for identifying a gene whose activation is effected by phosphorylated Smad-1 or Smad-5, comprising contacting a first sample of ALK-1 expressing cells that also express and phosphorylate Smad-1 or Smad-5 with an agent that inhibits or activates Alk-1.

> "Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention."

ATD Corp. v. Lydall, Inc. 48 USPQ2d 1321 (Fed. Cir. 1998)

The motivation to make the modifications suggested by the Examiner is based on applicants' own disclosure and not found in the cited art. The Examiner is using hindsight to pick and choose from the art and then suggesting various modifications to that art in an attempt to piece together applicants' invention.

While the Examiner speculates that Hopkins and Kohame might pique the interest of one of ordinary skill in the art to study vascular disease by developing a method that might resemble that which is claimed, the Examiner is applying at best an "obvious to try" standard, which has been rejected consistently as an inappropriate standard for determining obviousness under 35 U.S.C. § 103(a).

> An 'obvious to try situation exists when a general disclosure may pique the scientist's curiosity, such that further investigations might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued"

In re Eli Lilly & Co., 14 USPQ2d 1741 (Fed Cir. 1990)

In view of the forgoing remarks, it is clear the Kohame and Hopkins, alone or in combination, fail to render applicants' claim obvious and applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 28 under 35 U.S.C. § 103(a).

The foregoing amendments and remarks are made not for reasons of patentability but are meant to improve the understanding and clarity of the claims. They are not intended to limit the claims. Suggestions by the Examiner have been adopted where appropriate.

The Commissioner is hereby authorized to deduct any missing or insufficient fee from Deposit Account 06-2375, under Order No. 09901443.

Respectfully submitted,

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